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USING GENETIC INFORMATION TO SYNTHESIZE FUNCTIONAL GENE PRODUCTS / REVIEW ARTICLE

Dr. Haidar J. Muhammed[1], Dr.Ali R. Laftah[2],Dr. Abdalkader Saeed Latif[2], Estabraq Mohammed Ati[4]
1,2,4Department of Biology Science, Mustansiriyah University, POX 46079, Iraq-Baghdad.
3National University of Science and Technology / College of Health and Medical Technology
sthg@uomustansiriyah.edu.iq , ali.r.laftah@uomustansiriyah.edu.iq , abdalkaderlatif@yahoo.com

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Abstract:

We must answer some questions: What is gene expression? How does that happen? How is it diagnosed when talking about gene expression there is certainly a lot of information that may be missing or missed, were not able to reach it, as the rate of gene expression is linked to the rate of metabolic processes and the extent of the flow of all metabolites through certain pathways by regulating the formation or synthesis of specific enzymes for each gene, the rate of change in the activities of enzymes is present when essential substances are available. In contrast, enzymes required for biosynthesis are generally catabolic enzymes that are stimulated, catabolic enzymes are inhibited when metabolic products are present in the pathway in which they function.

Keywords: Gene expression, Functional Gene, Gene Regulation

A review Article Problem: Translated polypeptides undergo processing to form functional proteins. Adding or removing chemical groups can change the activity, stability, and localization of proteins in the cell, as the addition of ubiquitin groups leads to protein degradation. Thus, post-translational protein modifications are the final stage of gene regulation

A review Article Objective: There are causes of spatial and temporal differences during the expression of the same gene. Because current expression patterns depend strictly on previous expression patterns, there is a problem of regressively in the causes of the first differences in gene expression.

The method of the article: There are stages in which gene regulation takes place, including chromatin domains, transcription, and post-transcriptional modification and RNA transfer and translation.

1- INTRODUCTION

The term gene therapy entered the dictionary of commonly used vocabulary among researchers in the medical field before evidence of its effectiveness was provided, except in some individual cases and in passing. However, the abundance of information about this idea suggests many theoretical possibilities for its application, taking into account the many risks resulting from interference in the process of gene expression, which in reality appears more complex than can be imagined [1]. In general, it is known as those biological processes through which information from genes is converted into the synthesis of functional gene products, the most important of which are proteins. The rate of gene expression for genes varies according to their importance[2]. Products that are important are often expressed quickly and in large quantities to allow rapid growth, while genes that cells need under special conditions are not expressed to a large extent and in special conditions as well, rate of gene expression is linked to the rate of metabolic processes and the extent to which all metabolic materials flow in certain pathways[3]. It is controlled by regulating the formation or synthesis of specific enzymes for each gene and the rate of change in the activities of the enzymes present in them when basic materials are available, in return, synthetic enzymes. In general, catabolic enzymes are stimulated and inhibited when metabolites are present in the pathway in which they operate[4].

Gene expression is the basic feature in maintaining the integrity and functional coordination of the cell, which occurs in several ways, It falls under positive and negative regulation. This organization is represented in a prokaryotic group in which gene expression occurs, which begins with the process of mRNA transcription[5]. This is through the binding of proteins to each other through precise, specific sequence on a DNA strand that results in an increase or decrease in the rate of transcription in the eukaryotic community, mRNA cloning is very complex and has more than one mechanism in cells, this is achieved through processors for the regulation process. Here, gene expression and regulation are more specialized optional or alternative modification of the immature primary mRNA strand and the formation of several

different mRNA strands thus the process of translation occurs into various proteins related to the function of that cell. The mechanisms and effectiveness of regulation that affect expression processes across these genetic axes in general are based[6]. The efficiency rate at which the resulting mRNA is translated into a specific type of protein rate of speed and disintegration of mRNA molecules and rate of speed of transformation or transformation of proteins. The possibility of determining the effectiveness of the resulting proteins using covalent modification or an allosteric site[7].

1-1Regulation of gene expression

Simplifying the mechanism of protein synthesis by saying that it is simply the process of transcribing DNA into mRNA and translating the latter into ribosomes into proteins; It summarizes many basic and complex details, and it neglects to mention the mediation of various regulatory mechanisms[8].

Every cell of the organism contains the same genes, but only in certain cells, some genes express themselves, in other words, they are responsible for the synthesis of specific proteins specific to these cells. Transcription regulatory elements are located near the coding region of DNA and may be encountered on the upstream or downstream side of transcription. The regulatory element (which is part of the gene) located next to the site of upward transcription of the coding region is the start signal and is called the promoter. At a distance from it, where the DNA is linear, we find autonomic regulators that may be the enhancer that activates the promoter or the silencer that represses it[9].

The effectiveness of these elements is regulated by special proteins known as transcription factors (TFs), which have a distinctive structure, as they have the shape of a finger, which is formed as a result of the connection of a zinc atom with four amino acids (cysteine and/or histidine), which gives the polypeptide chain the appearance of a finger. Which allows it to fit into the grooves formed by the double helical structure of DNA[10]. This chain also includes leucine-leucine zipper bridges, which are variable-position bonds that result from a sequence of thirty-five amino acids, containing one leucine acid in every seven acids in it. This structure allows the protein to bend, forming dimers compatible with the DNA.

The upstream transcription complex includes several proteins, which consist of:

The transcription factor TFIID (Transcription Factor II D), which attaches to the promoter at the level of the TATA sequence rich in thymine and adenine nucleotides through the mediation of the TATA bonding protein (TBP), and from the associated transcription factor TFIIB (Transcription Factor II B). With the active enzyme RNA polymerase. The chromatin template modifies the activity of transcription factors through interaction between basic proteins (histones) and DNA. The degree of DNA methylation and changes in histones through acetylation are also involved. One of the most important post-transcriptional regulation mechanisms is splicing, which involves deleting non-coding introns from transcribed RNA and preserving coding exons adobe systems[11].

This process takes place within the cell nucleus and therefore RNA transcribed from the same gene can, depending on the function of the cells, undergo different splicing processes that produce different messenger RNAs, which ultimately leads to the synthesis of a different protein. Based on the gene itself, calcitonin can be synthesized in the thyroid gland, and CGRP (Calcitonin Gene Related Protein) in neurons, the mechanism of regulation is qualitative[12].

The formed mRNA migrates into the cytoplasm of the cell, passing through the holes in the nuclear membrane by an active energy-dependent transport mechanism. It is then translated into proteins. When it is fixed, it can be the same, and several times, the starting material in protein synthesis, that is, it can produce several molecules of the same corresponding protein, and here the mechanism of regulation is quantitative. Until now, the mechanism that ensures RNA stability is still unknown. The goal of this brief recollection of how proteins are synthesized is to show the complexity of this process, and to reach two slightly contradictory conclusions according [13]: The first is that the possibilities for genetic modification are endless. The second is the difficulty of arriving at special effects that are deliberately adapted to correct the disorders to be treated without causing undesirable effects.

1-2 Gene therapy principles

We have known, for many years, medications capable of altering the activity of genes, but they are not classified as genetic therapies. Sexual hormones, thyroid, insulin, and many vitamins, such as vitamin A, alter gene transcription, and some compounds, such as phenobarbital, stimulate gene transcription and the synthesis of many enzymes[14]. Gene therapy, in its narrow sense, is the replacement of a defective gene (a specific sequence of DNA) with another normal gene that encodes functional proteins that compensate for their missing or defective counterparts. The idea basically revolves around delivering a gene to the cell nucleus so that it becomes a source for the synthesis of a therapeutic protein, the presence of which is desirable in special disease cases. In its broadest sense, genetic therapy is the delivery of genetic material to the cell. It may be a gene or a piece of a gene, DNA or RNA, or a nucleotide combination as a processing medium[15]. The same name falls under the technology of neutralizing a specific DNA or messenger RNA sequence by introducing complementary DNAs or anti-sense RNAs that form complexes that are difficult to translate, two approaches to gene therapy: In vitro and in vivo. In the first method, in vitro, the target cells are harvested from tissue from the patient's body and transferred to nutrient media. After delivering the selected genetic material, they are returned to the patient's organs (Figure 3). The first use of this technology was to deliver the gene encoding the enzyme ADA (Adenosine desaminase) in lymphocytes, or within their blasts in the bone marrow of a patient suffering from a

deficiency of this enzyme. As for the in vivo method, Genetic material is delivered by intravenous or local injection, or by using aerosols to ensure that it reaches the target cell. It is worth noting that many nucleotide preparations have proven effective when given orally[16].

1-3Delivering genetic material

The genetic material that is to be introduced into the cell, the transport mechanisms are the same, given that cellular membranes are of a lipid nature and therefore impermeable to polar molecules such as DNA or RNA, so it was necessary to mediate vectors in order to deliver them to the cell, different types of vectors have been developed, each with a distinct specificity, because their benefits and limitations are mainly related to the clinical model. We mainly distinguish viral vectors, polymer-based particles of several types, and other vectors that rely on physical methods[17].

1-4 Viral vectors

Viruses are, naturally, excellent vehicles for delivering genetic material into the cell. Regardless of the type of virus used, the target cell is infected with the virus carrying the genetic material, with the emphasis being that, as a vector, it should be non-pathogenic and unable to replicate within the cell[18]. It should also not create immunity to the organism because this will cause many difficulties if the administration process is repeated. The most common conventional viruses used in genetic therapy applications are retroviruses, adenoviruses, and retroviral vectors were the first vectors used to deliver a gene into a cell. Although the viruses selected within this family are not pathogenic to humans, estimates indicate that the possibility of them multiplying in organisms is still possible. To solve this problem, special cells were developed in which recombinants, non-replicating viruses, are created. These cells are known as packaging cells, which are eukaryotes that have been genetically modified so that they include in their genome the three genes gag the viral structural proteins. It was deleted from the genome of the virus itself in order to prevent it from replicating within the organism, preserving the virus's ability to copy and express its genome, which contains the genetic treatment material. Thus, the recombinant cell is responsible for the synthesis of a large number of recombinant viruses that are safe for use in humans[19]. After administration of recombinants retroviral vectors, their RNAs are released in the target cells and converted, through the mediation of the enzyme retro transcriptase, into double-stranded DNA that merges with the cell genome, so that the cell is able to produce the desired protein by expressing the transgenic, which will be inherited to the daughter cells resulting from the division of the treated cell. From the above, we find that the problem of safety by following this approach is no longer a concern, but the disease cases that can be managed genetically using it are very limited, because retroviruses cannot transducer cells except in the stage of their division, and as a result they are useless in transuding quiescent cells such as neurons or slowly dividing cells, such as lung epithelium cells. Moreover, host cells are not capable, at least currently, of generating huge numbers of viruses that are sufficient to prepare concentrated preparations that produce a significant number of cells. The integration of the introduced genetic material into the cell genome may, in rare cases, activate the expression of one of the oncogenes, leading to carcinogenesis of the cell or at least disrupting the expression of one of the cells' normally functioning genes. Research is currently being conducted on lent viruses belonging to the retrovirus family because, unlike the first, they are distinguished by their ability to transducer both dormant and dividing cells[20].

1-5 Adenovirus as a vectors in gene therapy

The limited effectiveness of retroviruses and their many disadvantages are what rule them out, except in special cases, as carriers of genetic material. Therefore, research has turned to adenoviruses, which have proven experimentally to overcome many of the problems posed by their predecessors. Its most important advantage is its ability to transduce dormant cells in the organism itself without the need to biopsy and manipulate them in vitro and then restore them. It is the first option in the genetic treatment of cystic fibrosis, and unlike retroviruses, the genetic material transmitted through them does not integrate with the cellular genome[21]. The length of the transmitted sequence can also be increased by deleting a number of the original virus genes, such as E1A, E1B, E2, E3, and E4, according to the French team. Therefore, there is an almost universal possibility of replacing its original DNA with therapeutic sequences. However, we find major drawbacks, including the small space available for the conserved gene. Until now, there are no strains of host cells that provide sufficient numbers of the virus to prepare therapeutic doses.

The risk of causing an inflammatory reaction at the site of administration is also possible, as in most cases, these viruses cause stimulation of the immune system, especially when the dose is repeated, which is required to achieve a high transduction rate in the target cells and certain expression of the transferred gene[22].

1-6 Synthetic vectors

Many gene delivery methods rely on positively charged synthetic polymers, the most important of which is that they are soluble in water, in addition to their resistance to degradation first in the interstitial fluids and then within the cytoplasm of the target cell. Thus, this method made it possible to deliver the processed DNA into small-sized cages that cells could quickly capture. MIT has come up with an interesting method that uses nanoparticle-sized polymerization of positively charged cyclodextrin B grafted with PEG conjugated to adamantane, which enables the production of a DNA package that resists clumping (incorporation with serum proteins).) which makes them useless aggregates. In addition, this method

has enhanced the stability of the synthetic vector-DNA complex with the possibility of directing it towards specific cells through the introduction of specific ligands coupled to polyethylene glycol[23]. Perhaps the discovery in 1965 of the capabilities of liposomes made them, after years of research and development, one of the most widely used means of delivering DNA in the field of genetic therapy. An example is positively charged lipids of the type lipofectine, as these particles, whose size varies between 50 and 100 nanometers, Through its membrane, which is of a phospholipid nature, it is able to fuse into the cytoplasmic membrane of the target cell. Some protocols have licensed its use in gene therapy for melanoma, while the University of Utah used stearyl polylysine-based liposomes coated with low-density lipoprotein to transfer the gene encoding VEGF (Vascular Epithelial Growth Factor) to heart cells affected by ischemia, so that it was able to stimulate the growth of new blood vessels to reach Oxygen to deprived areas of the heart muscle. In the same context, both the University of Wisconsin-Madison and Cornell University found that biodegradable, positively charged soluble polymers based on polyaminoesters appear to be more beneficial than several non-viral vectors in terms of how well they bind to the transferred genetic material and how quickly they enter target cells[24].

1-7 Gene therapy mechanisms

Gene therapy is a method that holds great promise by delivering healthy genes to diseased cells. Although the introduced gene does not completely replace its defective or absent original counterpart; However, it can express itself by being transcribed and translated, giving the deficient protein or at least a new protein with therapeutic efficacy[25]. As a result of the above, we find that ensuring the proper delivery of the gene to the diseased cell is not sufficient alone. Rather, it must be confirmed that this gene will be transcribed and translated into the corresponding protein without interfering with the mechanism of other genes expressing themselves on the one hand, and that the amount of protein produced is sufficient and not excessive. Not a little on the other hand. Gene transfer can be applied to somatic cells or germinal cells alike, but for ethical reasons, performing genetic modifications on human germ cells is not legally permissible, and to this day it is still a matter of controversy among researchers and legislators. In this context, we can limit the application of genetic therapy to two main mechanisms according [26]:

A-Gene deficiency compensation

In many diseases that we have known for years, they are caused by a genetic defect; Drug treatment alone may not be sufficient, or may even be of no benefit at all. In genetic diseases resulting from a mutation in a specific gene, the potential of drug treatment is limited to alleviating the symptoms resulting from the absence of a functional protein encoded by the mutant gene. While the genetic treatment method holds the hope of finding a radical solution to the disease, by delivering a normal copy of the same gene to the diseased cells, the result being the synthesis of the deficient protein and the disappearance of the symptoms[27]. It is worth noting that ADA deficiency was the first disease condition to be licensed for treatment globally through therapeutic gene transfer, and the American researcher was the first to obtain this license in 1989 in the United States, the gene encoding the ADA enzyme leads to severe immunodeficiency that quickly leads to death upon exposure to the weakest pathogens. The reason is due to the accumulation of toxic metabolites in lymphocytes, in the bloodstream, which leads to their killing and thus the decline of immune defenses. According to an in vitro method, lymphocytes were harvested from the blood and genetically circulated by delivering the ADA gene through retroviruses as vectors, and then injected again, and a significant improvement in the clinical condition was observed, the problem that emerged is that the period of improvement is associated with the age of the genetically modified lymphocytes; Immune relapse will be renewed with the death of the treated lymphocytes, so simultaneous studies that took place in 1993 in France, the United States, and the United Kingdom resorted to harvesting lymphoblastoma cells from the bone marrow, modifying them, and then returning them to the patient's organs, so that, by their subsequent division, they give rise to normal lymphocytes that carry the ADA gene and achieve regular production of the enzyme throughout its life. . However, the initial results were not encouraging[28].

In the field of immunodeficiency diseases, genetic therapy has achieved remarkable effectiveness in managing some cases of severe combined immunodeficiency, known as X-SCID, because it is linked to the They have cellular immunity, which requires placing the infected child from birth in a sterile chamber, hence the name "bubble boy" disease, which occurs at a rate of one birth in every two hundred thousand globally, and five cases are recorded annually in France.

The disease is caused by a group of genetic abnormalities that cause significant dysfunction of the immune system, through a defect in the IL2RG gene on chromosome Xq13, which encodes the common gamma chain protein. In interleukin IL2 receptors, which leads to the complete absence of T lymphocytes and natural killer cells[29]. Until the beginning of 2000, bone marrow transplantation was the only treatment for the disease, which requires the presence of a suitable donor, and the rate of achieving this did not exceed 20%. On the other hand, the trend towards gene therapy began in France in 1993, which announced its first successes in April 2000 by adopting the technology of in vitro circulation of cells extracted from bone marrow with retroviruses carrying a functional copy of the defective gene, and then re-injecting them into the bloodstream. Complete recovery was achieved in two clinical cases. But in October 2002, the same research team announced the occurrence of leukemia in one of the ten treated cases, and then a second infection in 2003[30]. Following the first announcement, an American team that had adopted a similar technology

stopped all its clinical trials. Perhaps the reason is that the retroviral vector inserted a gene treatment near the promoter of the proto-oncogene LMO2, resulting in uncontrolled proliferation of clones of mature T lymphocytes. In light of this conviction, he from the Department of Gene Therapy Research at the University of Groningen stated that retroviruses seem to be the logical choice due to their relative ease in infecting bone marrow cells, but they can be replaced by other viral vectors such as lentiviruses or adenoviruses, or by synthetic vectors that serve the same purpose[31].

B-Neutralization of abnormal gene

Some special pathological cases, gene trafficking in cells can target the defective gene itself, which encodes a protein with a pathogenic effect, to prevent the expression of this gene. That is, the correction takes the DNA directly into the target cells. Perhaps the first methods that took this approach were the methods that used short oligonucleotides, which relied on the principle of triple helix formation. The triple helix strategy is based on the fact that the short, single-stranded chain forms a triple helix with DNA sequences (double-stranded) that are selectively attached within the DNA double-helix groove to the target sequences, which are either oligopurine or oligopyrimidine triple helix technology was developed with the aim of testing an anti-sense effect, because triplex-forming is often accompanied by inhibition of transcription of the target gene because short sequences trapped within the DNA can generate extra-chromatic mutations in it as a result of slowing down transcription that causes cellular correction that chimerical chains can extend chromosomal DNA so that they form a triple helix with it. This opens the door to the possibility of directing the nature of the mutation resulting from the formation of the triple helix, but the applications of this method are still very limited and are limited to isolating genes[32].

In the same context, a team reported that the transfer of chimeric RNA/DNA sequences complementary to fragments of the globin-coding gene allows the correction of 20% of homozygotes for the mutation in sickle cell anemia, the production of such chimeric chains was the result of studies in Philadelphia in 1996, which showed that the presence of RNA at the heart of the nucleotide chains stimulates the process of complementary duplication. In contrast, non-chimeric chains containing only DNA do not achieve a corrective effect[33]. The correction mechanism relies mainly on an exchange between the nucleotides of the chimerical chain and the nucleotides of cellular DNA. This technology achieved complete correction of the mutant gene in 7% of the cells that were circulated. According to the research team, the synthetic protein was specifically designed to help the vector virus insert the therapeutic gene into its correct position on the chromosome. However, the random cutting of another gene will create new problems. So it was safer to deal with the mRNA resulting from the transcription of the faulty gene rather than the gene itself. In this context, we can mention a genetic treatment strategy for TBD [30]. Cooley's disease, commonly known as thalassemia, where it is theoretically assumed that reducing the rate of translation of the messenger RNA of the alpha globin chain gene, by at least 20%, through degradation using an antisense nucleotide chain, leads to a significant improvement in the clinical condition. This strategy requires an H-nuclease capable of chopping the hybrid messenger RNA/nucleotide complex. A preliminary study has shown that this technology can be applied in cells that are circulated in vitro[34] .

2- CONCLUSIONS AND RECOMMENDATIONS

There are a number of therapeutic methods for cancer management based on gene immunotherapy. Based on the fact that tumor antigens are capable of causing an immune reaction that mediates the deletion of malignant cells, method has emerged based on increasing the antigenic capacity of tumor cells so that they elicit a stronger immune response that accelerates their clearance. Studies on models of syngeneic tumors in hemizygous mice have demonstrated a clear response to tumor mass, especially melanoma and kidney cancer, when a gene encoding cytokines such as interferon alpha (INF) is expressed or interleukin IL2 or the gene encoding the B7.1 molecule that interacts with the CD28 receptor located on the surfaces of lymphocytes.

Among the problems facing genetic treatment of tumors: Targeting tumor cells in the organoid, in a highly specific manner. A number of targeting strategies have been devised based on the physiological characteristics of solid tumors and their molecular environment, especially areas of necrosis and hypoxia, which have a high frequency of observation. This inspired the idea of reversing the phenotype of tumor cells by introducing the p53 tumor suppressor gene, which is located on the short arm of the first chromosome. As the p53 gene interferes with the expression of many genes in the cell, it stimulates the transcription of the p21 gene, which codes for the p21 protein, which inhibits a number of cyclines (proteins whose concentration changes depending on the cell cycle and which have essential roles in it), which means stopping the transcription of many genes and thus stopping cellular growth and prepare for death. The p53 gene suppresses the transcription of genes that inhibit this process, and also interferes in preventing the expression of genes encoding the oncoproteins c-fos and c-myc. Through this set of effects and other effects that were not mentioned, we find that the p53 gene suppresses the cell cycle and predisposes it to cell death. Therefore, several studies have been carried out based on the delivery of this gene in tumor cells through mediation.

A retroviral vector, especially in nasopharyngeal carcinoma and lung cancer. The results were encouraging, as they proved the theory that it is possible to treat tumors by accelerating the apoptosis of their cells. However, clinical applications of this theory are still, to date, ineffective due to the weak capacity of currently available delivery systems.

In fact, gene therapy, like other treatments, must prove its effectiveness, especially with regard to its immediate or long-term tolerability. But the biggest problem lies in developing safe and effective delivery systems that ensure the expression of the transferred treatment gene, without interfering with the expression of other genes. In any case, we are still at the beginning of a long and very complex chapter in the study of genetic modification, and we are very optimistic about the possibility of using genetic therapy in practice within the next few years.

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Corresponding Author:
Dr. Abdalkader Saeed Latif
National University of Science and Technology / College of Health and Medical Technology, Iraq.
Email: abdalkaderlatif@yahoo.com
ORCID: https://orcid.org/0000-0003-1901-9425

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